A wholly-owned subsidiary of Pfizer, Inc.

OPEN-LABEL SAFETY AND EFFICACY EVALUATION OF FX-1006A IN SUBJECTS WITH TRANSTHYRETIN (TTR) AMYLOIDOSIS

Compound:	Fx-1006A/PF-06291826
Compound Name (if applicable):	Tafamidis
US IND Number (if applicable):	74,866
European Clinical Trial Database (EudraCT) Number (if applicable):	2009-011535-12
Protocol Number:	Fx1A-303/B3461023
Phase:	3

The name, title, address and telephone number(s) of the sponsor's medical expert for the trial is documented in the study contact list located in the coordinator’s manual.

Document History

Document	Version Date	Summary of Changes
Amendment 2	05 June 2012	1. Protocol: extension of study duration to up to 10 years or until subject has access to tafamidis for TTR-FAP via prescription. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor. 2. Protocol – change in nomenclature for abbreviation of TTR-CM and TTR-FAP from ATTR-CM and ATTR-PN. 3. Protocol – change of term "patient" to "subject". 4. Protocol number – changed from Fx1A-303 to Fx1A-303/B3461023. 5. Renumbering of sections to align with standard Pfizer protocols:

Original section number	New section number
3.1	1.2
3.2	1.2.1
3.3.1	1.2.3
3.3.2	1.2.4
3.4	1.2.2
4	2.1
5.1	3
5.2	3.1
5.3	3.2
6.2	4.1
6.3	4.2
6.4	6.3
7.1	5.2.1
7.2	5.2.2
7.3	5.1
7.4	5.2.3
7.5	Removed
7.6	5.2.1
7.7	5.3
7.8	5.2.4
8, 8.1, 8.2, 8.3	6.1
8.4	6
8.5	7.3
8.6	7.2
8.7	7.6
8.8.1	5.4.1
8.8.2	5.4.2
8.9	7 (7.1– 7.7)
9 (9.1-9.12)	8 (8.1-8.12)
10 (10.1- 10.10)	9 (9.1-9.11)

		6. Section 1.1: Indication - Indication has been added 7. Section 1.2.4: Clinical Experience - update of Clinical experience to reflect most current IB 8. Section 2.2: Endpoints - section added 9. Section 3: Study design - abbreviated 10. Section 4.1: Inclusion Criteria – Inclusion of evidence of a signed informed consent document added 11. Section 4.2: Exclusion Criteria – added exclusion criteria • Males with partners of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for at least 3 months after last dose of investigational product 12. Section 4.3.1: Contraception – added section to increase clarity 13. Section 5.3: Drug Storage and Drug Accountability – updated to reflect most recent information on drug storage. 14. Section 6: Study Procedures – Addition of possibility for alternative options for study visits added 15. Sections 6.1, 6.2 added to increase clarity of required assessments and procedures to be performed at each telephone and clinic visit 16. Section 7.4: Assessments – electrocardiograms – ECGs added to protocol to be performed every 12 months. 17. Section 8 – Adverse Event Reporting – updated to reflect most updated requirements from Pfizer. 18. Section 9.10 – ECG analysis – added section 19. Section 9.11 – Interim analysis – added section 20. Sections 10, 11, 12, 13, 14, 15 – replace sections 11 and 12 from FoldRx protocol to reflect Pfizer requirements. 21. Appendix 4. Updated to remove Fold Rx and replace with Pfizer.

Amendment 1.1	27 June 2011	1. Company name update 2. Transfer of pharmacovigilance from ICON to Pfizer, Inc. (Exception: Argentina) 3. The compound "Fx-1006A" (research number) is "tafamidis meglumine" (20 mg soft gelatin capsule), thereafter referred to as simply, "tafamidis" 4. Name of chemical compound change: From: [N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate] To: [d-glucitol, 1-deoxy-1-(methylamino)-, 2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylate (1:1)] 5. Medical Monitor changed from PPD 6. FoldRx Protocol Approval Form: Updated protocol version and release date Updated Signatories for Regulatory/QA and Biostatistics. 7. Synopsis (Section 2), Sections 5.1, 6.4, 8.10, 8.11, 10.7.5, Appendix 1: Added text relating to assessment of ambulatory status: patient ambulation will be determined by the Investigator at every 6-month clinic visit and during each 3-month telephone follow-up (in between clinic visits), and at the end of study visit. 8. Synopsis (Section 2), Sections 3.4, 5.1, 8.5, 8.11, 10.6, Appendix 1: Added text relating to clinical laboratory testing that will involve blood samples taken at Baseline, every 6-month clinic visit, and at the end of study visit. 9. CCI [redacted] Qualified patients will be asked to provide written informed consent.

		10. Section 3.3: Updated Non-Clinical and Clinical summary information. 11. NEW - Sections 3.3.1 and 3.3.2: Created new sub-headings for Non-Clinical and Clinical Summaries, respectively, in Section 3.3. 12. Section 7.7: Updated storage conditions for investigational product. 13. Sections 8.10, 10.7.5, 14: Two new references added for the assessment of ambulation using the modified Polyneuropathy Disability (mPND) scoring system. 14. Section 9 (Adverse Events): Entire Section 9 updated per new procedures (Pfizer). SAE Reporting information updated from ICON (exception Argentina) to Pfizer, Inc. 15. Appendix 1 (Schedule of Events): Updated per Protocol Amendment. Visit windows added. CCI [redacted]
Original protocol	19 June 2009	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country Health Authorities, IRB/ERB, etc.

PROTOCOL SUMMARY

Indication:
Tafamidis is being developed for the treatment of transthyretin amyloidosis, specifically targeting TTR amyloid polyneuropathy and cardiomyopathy

Study Objectives:

- To obtain additional, long-term, open-label safety and efficacy data for tafamidis in subjects with transthyretin (TTR) familial amyloid polyneuropathy (TTR-FAP);
- To continue to provide the investigational product tafamidis to subjects with TTR-FAP who have completed Protocol Fx-006 or Protocol Fx1A-201.

Study Population:
Male and female subjects with TTR-FAP who have not undergone liver transplantation and who have completed Protocol Fx-006 (EudraCT 2008-001262-87) or Protocol Fx1A-201 (EudraCT 2007-006791-12). Up to 110 subjects are anticipated.

Test Product, Dose, and Mode of Administration:
Tafamidis 20 mg soft gelatin capsule once daily (at the same time each day).

Duration of Treatment: Up to 10 years or until subject has access to tafamidis for TTR-FAP via prescription. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. Such subjects are considered study completers. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor.

Clinical Endpoints:

Safety

The incidence of treatment-emergent adverse events (TEAEs), physical examinations, clinical laboratory testing, ECGs, use of concomitant medications, and vital signs.

Efficacy

- The Neuropathy Impairment Score (NIS);
- The Total Quality of Life (TQOL) score as measured using the Norfolk Quality of Life for diabetic neuropathy (QOL-DN) questionnaire;
- The Karnofsky Performance Scale Index;
- Assessment of subject ambulation.

Inclusion Criteria:

- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
- Subject has successfully completed either Protocol Fx-006 or Fx-1A-2011.
- If female, subject is post-menopausal, surgically sterilized, or willing to use an acceptable method of birth control (ie, hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide) throughout the study and for 3 months from the end of the study. (A condom alone is not considered an acceptable method of birth control).

- Male or female subjects with TTR-FAP who have not undergone liver or heart transplantation at time of enrollment and who have successfully completed Protocol Fx-006 or Protocol Fx1A-201.

Exclusion Criteria:

- Subject has not successfully completed either Protocol Fx-006 or Fx1A-201.
- Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 3 to 4 times/month. The following NSAIDs are allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.
- If female, subject is pregnant or breast feeding.
- Clinically significant medical condition that, in the opinion of the investigator, would place the subject at an increased risk to participate in the study.
- An ALT and AST value >3X ULN that in the medical judgment of the investigator is due to reduced liver function or active liver disease.
- The subject has received a liver or heart transplant at time of enrollment.
- Sexually active males with partners of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for at least 3 months after last dose of investigational product.

Study Design:

This is a Phase 3, open-label study designed to obtain additional, long-term, open-label safety and efficacy data for tafamidis and to continue to provide subjects with 20 mg oral tafamidis (soft gel capsule) who have completed either Protocol Fx-006 (a 1-year, open-label extension study to Protocol Fx-005 which is a randomized, double-blind, placebo-controlled, 18-month study to evaluate the safety and efficacy of tafamidis) or Protocol Fx1A-201 (a Phase 2, open-label study to evaluate TTR stabilization as well as the safety and tolerability of tafamidis) up to 10 years or until subject has access to tafamidis for TTR-FAP via prescription. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor.

Subjects who successfully complete Protocol Fx-006 or Fx1A-201 will report to the clinical unit on Day 0 (Baseline) to sign the informed consent form and determine their eligibility for Protocol Fx1A-303/B3461023. In addition, on Day 0 (Baseline), subjects will have their entrance criteria reviewed, medical history and demography for all subjects will be obtained. Relevant end of study assessments from Protocols Fx1A-201 and Fx-006 will serve as Baseline assessments for Protocol Fx1A-303/B3461023 if these examinations were performed within 30 days of Day 0 (Baseline). For any subject successfully completing Protocol Fx-006, the Karnofsky Performance Scale Index will be assessed and the cranial nerve and upper limb components of the NIS will be performed and combined with the NIS-LL data from the end of study visit from Protocol Fx-006.

If there is more than 30 days between the final study visit of Fx-006 or Fx1A-201 and Day 0 (Baseline) of Fx1A-303/B3461023, all Day 0 study procedures will be performed (ie, no data from the final study visits from the previous studies will be utilized).

Eligible subjects will begin once-daily dosing with 20 mg tafamidis at home on Day 1 (ie, first dose) and will return to the clinical unit for study visits every 6 months.

Adverse events (AEs) and concomitant medication use will be collected at each 6-month visit to the clinical unit and, if female, a urine pregnancy test will be performed. Clinical laboratory testing will also occur at every 6-month visit and subject ambulation status will be determined by the Investigator at these visits. ECGs will be obtained annually.

A telephone call will be made at 3-month intervals between clinic visits to assess safety, the use of concomitant medications, pregnancy, and to assess subject ambulatory.

For the evaluation of efficacy, the NIS, Norfolk QOL-DN, and Karnofsky Performance Scale Index will be performed on an annual basis (ie, every other 6-month visit).

CCI [redacted]

An end of study visit to assess safety and efficacy will occur upon subject withdrawal (for any reason), program discontinuation by the Sponsor, or upon completion of the study.

Statistical Methods:
Descriptive statistics will be used for this open-label study; the long-term effect of tafamidis on clinical outcomes as measured by NIS, NIS-LL, Norfolk QOL-DN, and subject ambulation will be explored. All demographic, clinical laboratory, concomitant medications, vital signs/physical examinations, ECGs and AE data collected will be presented in data listings. An interim analyses will be performed during the course of the study to allow for the reporting of safety and efficacy data to the scientific community through presentation at scientific and professional meetings.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Procedure/Evaluation	End of study visit from Fx-006 or Fx1A-201 and/or **Day 0 (Baseline)**[a]	Open-label Investigational Product				End of study visit[g]
		Day 1	Telephone contact (every 3 months between clinic visits)	Clinic visits (every 6 months other than 12 month visits)	Clinic visits (every 12 months)	
Visit windows:		**±1 week**	**±1 week**	**±2 weeks**	**±2 weeks**	**±2 weeks**
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographics	X					
Medical history	X					
Physical examination	X[b]				X[b]	X
Blood sample for laboratory testing[c]				X	X	X
Assessment of ambulatory status (mPND)			X	X	X	X
Urine test for pregnancy[d]	X			X	X	X
Pregnancy determination[d]			X			
Enrollment	X					
Dispense tafamidis[e]	X		X	X	X	
First dose of tafamidis		X				
Tafamidis compliance and accountability				X	X	X
NIS[f]	X				X	X
Norfolk QOL-DN[f]	X				X	X
Karnofsky Performance Scale Index[f]	X				X	X
ECG					X	X
Adverse events	X		X	X	X	X
Concomitant medication	X		X	X	X	X

[a] Relevant data from the end of study visits from Protocols Fx-006 and Fx1A-201 will be used for Day 0 (Baseline) if evaluations were performed within 30 days of Day 0.

[b] The end of study physical examination (including weight and vital signs) from Protocols Fx-006 and Fx1A-201 will serve as Day 0 (Baseline) for Protocol Fx1A-303/B3461023 if these examinations were performed within 30 days of Day 0. An abbreviated physical examination (including weight and vital signs) will be conducted at every other 6-month visit. For blood pressure and pulse, measurements will be taken lying and standing.

[c] Laboratory tests listed in Section 7.3.

[d] Subjects with a positive result will be excluded or discontinued. Urine pregnancy test will be done at all clinic visits, subjects will be asked about potential pregnancies on phone contacts.

[e] If determined to be eligible, subjects will be given a 3-month supply of investigational product on Day 0 (Baseline) for self-administration at home beginning on Day 1 (i.e., first dose). Subjects will return to the clinical unit every 6 months and will receive a 3-month supply of investigational product at each visit for self-administration at home. At 3-month intervals between clinic visits, 3-month supplies of investigational product will be mailed directly to subjects from the clinical site.

[f] For subjects who successfully completed Protocol Fx1A-201, the NIS, Norfolk QOL-DN, and Karnofsky scores from the end of study visit of Protocol Fx1A-201 will serve as Day 0 (Baseline) assessments for Protocol Fx1A-303/B3461023 if these procedures were performed within 30 days of Day 0. For subjects who successfully completed Protocol Fx-006, the Norfolk QOL-DN from the end of study visit from Protocol Fx-006 will serve as Day 0 (Baseline) if it was performed within 30 days of Day 0. In addition, the cranial nerve and upper limb components of the NIS will be performed on Day 0 (Baseline) and combined with the NIS-LL data from the end of study visit from Protocol Fx-006 and the Karnofsky Performance Scale Index will be assessed on Day 0 (Baseline) of Protocol Fx1A-303/B3461023.

TABLE OF CONTENTS

LIST OF TABLES 14
1. INTRODUCTION 18
1.1. Indication 18
1.2. Background and Rationale 18
1.2.1. Tafamidis for the Treatment of TTR-FAP 19
1.2.2. Study Rationale 19
1.2.3. Non-Clinical Experience of Tafamidis 20
1.2.4. Tafamidis (Fx-1006A) Clinical Experience 23
2. STUDY OBJECTIVES AND ENDPOINTS 25
2.1. Objectives 25
2.2. Endpoints 25
3. STUDY DESIGN 25
3.1. Rationale for Study Design and Control Group 26
3.2. Study Duration and Dates 26
4. SUBJECT SELECTION 26
4.1. Inclusion Criteria 26
4.2. Exclusion Criteria 27
4.3. Life Style Guidelines 27
4.3.1. Contraception 27
5. STUDY TREATMENTS 28
5.1. Allocation to Treatment 28
5.2. Drug Supplies 28
5.2.1. Formulation and Packaging 28
5.2.2. Preparation and Dispensing 28
5.2.3. Administration 29
5.2.4. Compliance 29
5.3. Drug Storage and Drug Accountability 30
5.4. Concomitant Medication(s) 30
5.4.1. Allowed Medications 30
5.4.2. Medication Restrictions 30

6. STUDY PROCEDURES 31
6.1. Screening/Baseline Assessment 31
6.2. Study Period 32
6.2.1. Months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, 105, 111, 117 32
6.2.2. Months 6, 18, 30, 42, 54, 66, 78, 90, 102, 114 33
6.2.3. Months 12, 24, 36, 48, 60, 72, 84, 96, 108 33
6.2.4. End of Study Visit 34
6.3. Subject Withdrawal 35
7. ASSESSMENTS 36
7.1. Efficacy Assessments 36
7.2. Pregnancy 37
7.3. Clinical Laboratory Tests 38
7.4. Electrocardiograms 39
7.5. Physical Examinations and Vital Signs 39
7.6. Adverse Events 39
7.7. Concomitant Medications 39
8. ADVERSE EVENT REPORTING 39
8.1. Adverse Events 39
8.2. Reporting Period 40
8.3. Definition of an Adverse Event 40
8.4. Abnormal Test Findings 41
8.5. Serious Adverse Events 41
8.5.1. Potential Cases of Drug-Induced Liver Injury 42
8.6. Hospitalization 43
8.7. Severity Assessment 44
8.8. Causality Assessment 44
8.9. Exposure During Pregnancy 45
8.10. Withdrawal Due to Adverse Events (See Also Section 6.3) 46
8.11. Eliciting Adverse Event Information 46
8.12. Reporting Requirements 46
8.12.1. Serious Adverse Event Reporting Requirements 47

8.12.2. Non-Serious Adverse Event Reporting Requirements 47
8.12.3. Sponsor Reporting Requirements to Regulatory Authorities 47
9. DATA ANALYSIS/STATISTICAL METHODS 47
9.1. Sample Size Determination 48
9.2. Efficacy Analysis 48
9.2.1. Analysis of Primary Endpoint 48
9.2.2. NIS-LL 48
9.2.3. NIS 48
9.2.4. Norfolk QOL-DN 48
9.2.5. Karnofsky Performance Scale Index 49
9.2.6. Ambulatory Status 49
CCI
9.4. Demographics and Baseline Characteristics 49
9.5. Physical Examination and Vital Signs 49
9.6. Clinical Laboratory Testing 49
9.7. Adverse Events 49
9.8. Concomitant Medication 49
9.9. Pregnancy 50
9.10. ECGs 50
9.11. Interim Analysis 50
9.12. Data Monitoring Committee 50
10. QUALITY CONTROL AND QUALITY ASSURANCE 50
11. DATA HANDLING AND RECORD KEEPING 50
11.1. Case Report Forms/Electronic Data Record 50
11.2. Record Retention 51
12. ETHICS 52
12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 52
12.2. Ethical Conduct of the Study 52
12.3. Subject Information and Consent 52
12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 53
13. DEFINITION OF END OF TRIAL 53

13.1. End of Trial in a Member State 53
13.2. End of Trial in all Participating Countries 53
14. SPONSOR DISCONTINUATION CRITERIA 53
15. PUBLICATION OF STUDY RESULTS 53
15.1. Communication of Results by Pfizer 54
15.2. Publications by Investigators 54
16. REFERENCES 56

LIST OF TABLES

Table 1. Most Common (≥5% in Tafamidis Treatment Group) Treatment-Emergent Adverse Events Reported at a Higher Incidence for Tafamidis Than Placebo – TTR-FAP Patients in Study Fx-005 24

APPENDICES

CCI [redacted]

ABBREVIATIONS

Abbreviation	Definition
ADL	activities of daily living
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATTR	TTR amyloidosis
TTR-CM	TTR with cardiomyopathy
TTR-FAP	TTR with polyneuropathy
AUC	area under the concentration-time curve
BLQ	below the limit of quantification
bpm	beats per minute
C	Celsius
Cl	clearance
cm	centimeter
CMAP	compound muscle action potential amplitude
C_{max}	maximum plasma concentration
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation; conduction velocity
dL	deciliter
DML	distal motor latency
DN	diabetic neuropathy
DPN	diabetic polyneuropathy
EC	ethics committee
ECG	electrocardiogram
FAP	familial amyloid polyneuropathy
FDA	Food and Drug Administration
GCP	good clinical practice
Glu89Gln	glutamic acid replaced by glutamine at position 89
Gly47Ala	glycine replaced by alanine at position 47
Gly47Glu	glycine replaced by glutamic acid at position 47
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
HRDB	heart rate response to deep breathing
ICH	International Conference on Harmonisation
Ile107Met	isoleucine replaced by methionine at position 107
Ile84Thr	isoleucine replaced by threonine at position 84
Ile107Val	isoleucine replaced by valine at position 107

Abbreviation	Definition
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
K EDTA	potassium edetic acid
kg	kilogram
Leu55Arg	leucine replaced by arginine at position 55
Leu58His	leucine replaced by histidine at position 58
LFTs	Liver function tests
LLN	lower limit of normal
LLQ	lower limit of quantification
Lys70Asn	lysine replaced by asparagine at position 70
mBMI	modified body mass index
mPND	Modified polyneuropathy disability
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
µg	microgram
µM	micromolar
mL	milliliter
NCI	National Cancer Institute
NCS	nerve conduction studies
NIS	Neuropathy Impairment Score
NIS-LL	Neuropathy Impairment Score – Lower Limb
nM	nanomolar
NOAEL	no observable adverse effect level
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OTC	over-the-counter
PK	pharmacokinetic
PT	prothrombin time or preferred term
SRSD	Single reference safety document
QOL	quality of life
SAE	serious adverse event
Ser77Phe	serine replaced by phenylalanine at position 77
Ser77Tyr	serine replaced by tyrosine at position 77
SF-36	Short-form 36
SOC	system organ class
$t_{1/2}$	half-life
T_4	thyroxine
Thr49Ala	threonine replaced by alanine at position 49
Thr60Ala	threonine replaced by alanine at position 60
T_{max}	time to maximum plasma concentration
TPGS	d-alpha-tocopherol polyethylene glycol 1000 succinate

Abbreviation	Definition
TQOL	total quality of life
TSH	thyroid-stimulating hormone
TTR	transthyretin
Tyr114Cys	tyrosine replaced by cysteine at position 114
ULN	upper limit of normal
Val30Ala	valine replaced by alanine at position 30
V30M	valine replaced by methionine at position 30
WBC	white blood cell

1. INTRODUCTION

1.1. Indication

Tafamidis is being developed for the treatment of transthyretin amyloidosis, specifically targeting ATTR polyneuropathy and cardiomyopathy. This protocol will be specific for the ATTR polyneuropathy (TTR-FAP) indication.

Marketing authorization for TTR-FAP was granted in the European Union on 16 November 2011 for the indication of treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay neurologic impairment.

1.2. Background and Rationale

Transthyretin amyloidosis is a disease induced by accumulation of insoluble fibrillar protein as amyloid, in the tissues in amounts sufficient to impair normal function. The major phenotypic presentations are a sensorimotor and autonomic neuropathy (ATTR with polyneuropathy, or TTR-FAP) and restrictive cardiomyopathy (ATTR with cardiomyopathy, or TTR-CM). Transthyretin, a 127-amino acid, 55 kDa protein, primarily synthesized in the liver, is a secreted protein present in the blood and cerebrospinal fluid and is a carrier of thyroxine and retinol-binding protein-retinol (vitamin A) complex.[1, 2] In its native state, TTR exists as a homotetramer with two C2 symmetric funnel-shaped thyroxine binding sites located at the central dimer-dimer interface.

Natural amino acid sequence (wild-type) TTR and mutated variants of TTR can be involved in amyloid disease. However, mutated TTR species are more prone to accelerated fibrillogenesis, the most important risk factor for TTR amyloidosis.[1, 2] There are more than 80 TTR point mutations that have been associated with TTR amyloidosis.[3] All disease-associated mutations characterized thus far destabilize the TTR tetramer and many influence the velocity of rate-limiting tetramer dissociation.[4] An amyloidogenic mutation or aging can lead to tetramer dissociation into an alternatively folded monomeric amyloidogenic intermediate. This intermediate self-assembles into profilaments, filaments, and, under certain conditions, amyloid fibrils.[4, 5] In fact, the rate determining step for TTR amyloid formation is tetramer dissociation.[6]

V30M is the most common mutation associated with TTR-FAP, with major foci of patients in Portugal, Sweden and Japan. The disease usually begins in the third or fourth decade, but the onset of symptoms may be later, particularly in Sweden. Initial symptoms include decrease in temperature and pain sensation in the lower extremities; autonomic dysfunction, including orthostatic hypotension, gastrointestinal motility disorders, impotence, and urinary retention/incontinence. As the disease progresses to involve larger myelinated fibers, muscle weakness, loss of reflexes, and the impairment of position and vibratory sensations can occur. At this stage, involvement of upper extremities becomes apparent. Although penetrance varies greatly among geographic and ethnic foci, the outcome of TTR-FAP is invariably progressive and fatal.[7, 8] The length of survival for patients with TTR-FAP is severely shortened. After a mean interval of 10 years from initial symptom, patients usually

die from progressive and relentless worsening of the neuropathy, secondary infections, cachexia or sudden death.[7] The only currently available disease-modifying treatment option is liver transplant.

1.2.1. Tafamidis for the Treatment of TTR-FAP

Pfizer, Inc. is currently investigating tafamidis meglumine (Fx-1006A) for the treatment of TTR-FAP. Tafamidis meglumine, d-glucitol, 1-deoxy-1-(methylamino)-, 2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylate (1:1), is the meglumine salt form of tafamidis (Fx-1006), 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid, a novel, small molecule stabilizer of transthyretin. Specifically, tafamidis exhibits non-cooperative binding (ie, dissociation constants of 2 nM [K_{d1}] and 154 nM [K_{d2}], respectively) to the two thyroxine binding sites on the native tetrameric form of TTR and thereby prevents its dissociation into monomers. At low pH, fibril formation of wild-type TTR and the most prevalent amyloidogenic variants, V30M and V122I, is potently inhibited by tafamidis. No fibril formation is observed for wild-type, V30M, and V122I variants at a 2:1 tafamidis: TTR stoichiometry. Under urea denaturating conditions, only 33% of TTR tetramer dissociates after incubation for 72 hours with equimolar quantity of tafamidis, when negligible tetramer dissociation is observed at a 2:1 tafamidis:TTR stoichiometry. Based on these data, it appears that a 1:1 tafamidis:TTR stoichiometry should be sufficient to stabilize TTR. The normal range of TTR level is between 18 and 38 mg/dL, corresponding to 3.2 to 6.8 μM of TTR. Therefore, plasma level of 3.6 to 7.2 μM (~1-2 μg/mL) of tafamidis should stabilize TTR levels at least to the upper limit of the normal range.

In vitro addition of tafamidis and tafamidis meglumine to human plasma stabilizes wild-type, V30M, and V122I tetrameric TTR under strong urea denaturing conditions for at least 4 days. Under these same conditions most of the TTR is denatured in 2 days in the absence of stabilizer. Stabilization is observed at tafamidis concentrations between 3.6 and 7.2 μM for TTR plasma levels ranging from low [15.5 mg/dL (2.8 λM)] to high [28 mg/dL (5 μM)], confirming the effective therapeutic plasma level range between 3.6 and 7.2 μM (corresponding to ~1-2 μg/mL concentration of tafamidis in plasma). Ex-vivo results with plasma samples from initial Phase 1 clinical testing confirm this hypothesis and indicate that drug plasma levels between 0.7 to 1.7 μg/mL stabilize plasma TTR (when TTR plasma levels are between 16 and 36 mg/dL) after once a day dosing with tafamidis meglumine. Based on Phase 1 results, this drug level range would be achieved at steady-state after once-daily 20 mg (soft gel capsule), the tafamidis meglumine dose chosen for clinical evaluation.

Refer to the tafamidis (Fx-1006A) Investigator Brochure for further information.

1.2.2. Study Rationale

This current study is being conducted to obtain additional safety and efficacy data and to provide continued dosing of tafamidis for up to 10 years, or until subject has access to tafamidis for TTR-FAP via prescription, to patients with TTR-FAP who have not undergone liver or heart transplantation and who have completed either Protocol Fx-006 (EudraCT

2008-001262-87) or Protocol Fx1A-201 (EudraCT 2007-006791-12), as described above. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor (see Section 6.3). Subjects will continue to receive once-daily 20 mg tafamidis. Safety will be assessed via the incidence of treatment-emergent AEs, the use of concomitant medications, and by results from clinical laboratory testing, physical examinations, ECGs, and vital signs.

Prior to enrollment in this current study, subjects who complete Protocol Fx-006 will have received study medication for a total of 30 months (18 months of double-blinded treatment in Protocol Fx-005 plus 12 months of open-label treatment in Protocol Fx-006); subjects who complete Protocol Fx1A-201 will have received open-label tafamidis for 12 months.

1.2.3. Non-Clinical Experience of Tafamidis

Nonclinical pharmacology, pharmacokinetic (absorption, distribution, metabolism, and excretion; ADME), and toxicology studies conducted both in vitro and in vivo in the mouse, rat, rabbit, and dog have been completed. In vitro nonclinical studies have confirmed that the pharmacological activity of tafamidis is consistent with its high affinity binding to the two thyroxine binding sites of TTR in a non-cooperative manner and the resulting stabilization of TTR (wild type and amyloidogenic variants) by preventing dissociation of tetramers into monomers.

The general safety pharmacology profile of tafamidis demonstrated minimal nonselective binding to enzymes or ion channels, with no potential for anti-inflammatory activity. Tafamidis had minimal effects on either the central nervous system or cardiopulmonary physiology parameters in dogs. Tafamidis did not demonstrate the potential for QT prolongation. QTc shortening, observed at doses of 100 and 300 mg/kg, was associated with total plasma concentrations that exceeded 90 µg/mL. However, mean human steady-state maximum concentration (C_{max}) values following the daily therapeutic dose of 20 mg in elderly and nonelderly subjects were 2.8 and 2.3 µg/mL respectively. Given the 30 to 40-fold difference in exposures, it is felt that the nonclinical observations have little relevance to the clinical profile of tafamidis.

Predictable pharmacokinetic behavior of tafamidis was demonstrated following oral administration in the nonclinical species. Tafamidis was absorbed following oral administration with an absolute bioavailability >90% and exhibited dose proportional increases in C_{max} and AUC at dose up to 30 mg/kg, but further increases in the administered dose provided less than proportional increases in systemic exposure, indicating saturation in the drug absorption. Terminal plasma half life is about 40 hours following a single administration. Drug accumulation has been confirmed in repeated dose studies.

Tafamidis is readily absorbed through the intestinal wall upon administration and is bound to a high extent to plasma proteins (>97%), essentially TTR and albumin. Tafamidis distributes widely in tissues (maternal and fetal), crosses the placental barrier to an extent of less than 5% of the initial dose, and ~ 30% of the dam's dose transferred into the milk.

Tafamidis demonstrated a high degree of metabolic stability and its limited biotransformation resulted in the formation of a monoglucuronide (acylglucuronide) as the primary metabolite in most of the nonclinical species and humans, while a monooxidative product was only detected in the mouse and rabbit. In rats, tafamidis is cleared primarily via biliary excretion and fecal elimination with some enterohepatic circulation, with a smaller contribution by the urine. A human ADME study suggests similar pathways are operative in humans.

Tafamidis meglumine has been evaluated in vitro to assess protein binding, induction and inhibition of cytochrome P450 enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5), and inhibition of transporter protein P glycoprotein (P gp), with results suggesting very low likelihood for clinical drug-drug interactions. No significant CYP 450 inhibition was observed. A series of nonclinical toxicity studies were conducted in mice, rats, and dogs to assess the safety of tafamidis. The absence of acute toxicity following a single dose of tafamidis up to 600 mg/kg in dogs is indicative of a low risk for overdose. Tafamidis was well tolerated following repeated daily oral administration up to 26 weeks in rats and 39 weeks in dogs. The NOAEL was determined to be 30 mg/kg/day in the rat and 45 mg/kg/day in dog. When doses were increased above the NOAELs, rodents had a drug accumulation in their stomachs while dogs vomited. Other signs of toxicity accompanied these obvious signs, including decreased food intake, modified feces, stress related signs, increase in liver weight and in liver enzyme levels, lymphoid depletion, and kidney lesions in rodents.

Tafamidis was nongenotoxic in a battery of in vitro studies, although a slight increase in frequency of polyploid cells was observed at 100 and 200 µg/mL in the presence of S9 activation but not without metabolic activation in the in vitro chromosome aberration assay using human peripheral lymphocytes. Polyploidy is not considered to be a reliable surrogate marker for aneugenicity. The lack of risk for aneuploidy induction with tafamidis was further evidenced by the lack of micronucleus induction in the bone marrow of Sprague-Dawley rats at the doses producing C_{max} and AUC values significantly exceeding the predicted clinical exposures (~ 72X over the C_{max} and ~ 67X over the steady state $AUC_{(0-24)}$ observed in humans, based on exposure in a 4-week rat study). The evaluation of the carcinogenic potential in hemizygous Tg.rasH2 mice did not demonstrate an increase in the incidence of neoplasia.

Tafamidis did not demonstrate any effects on fertility, general reproductive performance and early embryo-fetal development in the rat and the maternal and paternal NOEL for reproductive toxicity was determined to be greater than 30 mg/kg/day. Developmental toxicity was evident in the rat by reduced fetal weights in the 30 and 45 mg/kg/day maternal dosage groups (developmental NOAEL = 15 mg/kg). Developmental toxicity in the rabbit was demonstrated by increased post-implantation loss, reduced fetal body weight and associated skeletal variations, and malformation at 8 mg/kg and skelatal variations at

2 mg/kg/day. The NOEL for developmental toxicity in rabbits was 0.5 mg/kg/day. Tafamidis-related toxicity in the developmental and perinatal/postnatal reproduction toxicity study in rats resulted in a NOAEL for reproductive toxicity and for viability and growth of the F1 generation of 5 mg/kg/day. Women of child-bearing potential should take measures to prevent pregnancy while being treated with tafamidis.

Non-clinical data indicate that there is a large safety margin above the anticipated human efficacious plasma concentration and those concentrations associated with toxicity in rats or dogs. Emesis was the most common form of clinical intolerance in the dog. Owing to the dosing strategy, the immediate emetic activity led to apparent aspiration of gastric contents and/or drug, leading to moribundity and subsequent euthanasia. The gastric impaction and subsequent delayed gastric emptying, presumably followed by circulatory distress, shock and multiorgan failure, in rats was caused by a supraclinical dosing regimen and is not a relevant risk to human subjects. While the exact mechanism(s) for the toxicities observed following the oral administration of tafamidis has not been elucidated, there is an ample therapeutic margin to permit safe exposure to humans and there was no toxicity identified that would preclude human use, such as undetectable lesions or irreversible damage.

No target organs of tafamidis-related toxicity were identified in the repeated dose toxicity studies conducted in rats or dogs (26 weeks and 39 weeks, respectively). However, in the CByB6F1 hybrid mouse and the tg.rasH2 mouse, the liver and/or kidney have been identified as target organs as non-neoplastic lesions were noted following treatment for 28 days (CByB6F1 hybrid mouse) or 26 weeks (tg.rasH2 mouse). Nephrosis was the primary lesion noted in the kidneys, only in male mice and in a dose-dependent manner. In the liver, centrilobular hypertrophy and scattered single cell necrosis were present in male mice more than in the female mice in terms of the incidence of both lesions and the severity of the centrilobular hypertrophy. The incidence of both liver lesions was dose dependent. However, the mouse (CByB6F1) did not demonstrate a unique monooxide metabolite that was not present in the rat or dog, nor has it been detected in the plasma of humans administered tafamidis. However, a causal relationship between the monoxide metabolite and the liver and/or kidney lesions has not been established.

Generally, there were no significant toxicities observed in the repeated dose toxicology studies in the rat and dog. Therefore, tafamidis was considered to be well tolerated in the rat at dose levels up to 30 mg/kg/day for 26 weeks, providing an exposure ratio of 45- to 63-fold based on the human AUC at steady state, and in the dog at dose levels up to 45 mg/kg/day for 39 weeks providing an exposure ratio of 29- to 36-fold based on the human AUC at steady state. Additionally, there was no evidence for an increased risk of neoplasia at exposures at least 31-fold the human AUC nor was there evidence of any tafamidis-related genotoxicity. With the exception of the reproductive developmental toxicity findings, tafamidis has an excellent nonclinical safety profile.

Refer to the tafamidis Investigator Brochure for further details.

1.2.4. Tafamidis (Fx-1006A) Clinical Experience

The clinical development program for tafamidis has included 13 controlled and uncontrolled clinical trials and two non-interventional, observational studies. As of 13 May 2011, patients with TTR-FAP (n=127) received 20 mg of tafamidis administered daily for an average of 538 days (range of 15 to 994 days) or approximately 187 patient-years. The mean duration of exposure was 17.7 months: 87 were treated for at least 1 year, 43 were treated for at least 2 years, and 31 were treated for at least 30-<36 months.

The tafamidis 20 mg soft gelatin capsule (as used in the clinical studies) demonstrated a half-life average of 59 hours and $C_{avg(SS)}$ average of 2.07 µg/mL (SD=0.20). The tafamidis 20-mg soft gelatin capsule daily dose resulted in an average fluctuation (peak to trough) of 51.8%, with an average minimum concentration (C_{min}) of 1.61 µg/mL and an average C_{max} of 2.66 µg/mL. The average range was consistent with the 1 to 2 µg/mL required to stabilize the TTR tetramer; steady state was attained within 12 days, and exposure was consistent across subjects, with low variability across subjects for key PK parameters. Note that steady-state exposure was similar between males and females. Therefore, the 20 mg daily dose has been used in the development program.

The primary purpose of a therapy such as tafamidis is to stabilize the TTR tetramer, thus inhibiting the amyloid cascade and ultimately halting or slowing TTR-FAP disease progression over a sustained period of time. During the 18-month period of intervention in Study Fx-005, tafamidis slowed the course of neurological impairment and maintained quality of life in treated patients. Together, with the extension Study Fx-006 data, tafamidis demonstrated a sustained effect over 30 months, a period of time representing approximately 25% of the average TTR-FAP disease duration of 10 years. Further, Study Fx1A-201 was a small Phase II open label, single-treatment arm study designed primarily to determine the efficacy of tafamidis in stabilizing TTR variants other than the V30M (valine replaced by methionine at position 30) mutation. The results from this study of non-V30M TTR-FAP patients, which represented an older, more severely affected patient population, strongly supported the observed efficacy of tafamidis in V30M patients. As in Study Fx-005, the consistency of response across endpoints measuring different aspects of this multi-faceted disease was again observed following 12 months treatment with tafamidis. The results indicated the disease-modifying utility of tafamidis in treating all patients with TTR-FAP, regardless of mutation.

TTR-FAP is a rare disorder. The safety data described reflect exposure of 127 TTR-FAP patients to 20 mg of tafamidis administered daily for an average of 538 days (ranging from 15 to 994 days). The population was composed of adult patients diagnosed with symptomatic TTR-FAP, with a mean age of approximately 44 years; approximately half of the patients were female, and approximately 90% of the patients were Caucasian. Note that primary evidence of safety and efficacy was obtained from a placebo-controlled 18-month study in patients with TTR-FAP. Table 1 provides a summary of the most common TEAEs (≥5% in tafamidis treatment group) and reported at a higher incidence in tafamidis than in placebo during the pivotal Phase 2/3 study (Study Fx-005).

Table 1. Most Common (≥5% in Tafamidis Treatment Group) Treatment-Emergent Adverse Events Reported at a Higher Incidence for Tafamidis Than Placebo – TTR-FAP Patients in Study Fx-005

	Fx-005	
MedDRA Preferred Term	Tafamidis (N=65) n (%)	Placebo (N=63) n (%)
Patients With At Least One Event	60 (92.3)	61 (96.8)
Diarrhoea	17 (26.2)	11 (17.5)
Urinary tract infection	15 (23.1)	8 (12.7)
Pain in extremity	11 (16.9)	6 (9.5)
Influenza	10 (15.4)	9 (14.3)
Nasopharyngitis	9 (13.8)	8 (12.7)
Abdominal pain upper	8 (12.3)	2 (3.2)
Back pain	5 (7.7)	4 (6.3)
Punctate keratitis	5 (7.7)	3 (4.8)
Myalgia	5 (7.7)	2 (3.2)
Upper respiratory tract infection	4 (6.2)	3 (4.8)
Anxiety	4 (6.2)	3 (4.8)
Depression	4 (6.2)	3 (4.8)
Vaginal infection	4 (6.2)	1(1.6)

There were no meaningful changes in vital signs, clinical laboratory parameters, ECG parameters (including QTc interval), or other safety parameters measured. No meaningful changes in echocardiogram and ECG were observed for patients with a medical history of cardiomyopathy. Tafamidis has been well tolerated by both healthy subjects during the Phase I clinical studies as well as in patients during the Phase II and III clinical studies.

The primary purpose of a therapy such as tafamidis is to stabilize the TTR tetramer, thus inhibiting the amyloid cascade and ultimately halting or slowing TTR-FAP disease progression over a sustained period of time. During the 18-month period of intervention in Study Fx-005, tafamidis significantly and consistently altered the course of neurological impairment and maintained quality of life in treated patients across multiple measures of treatment efficacy. Together, with the extension Study Fx-006 data, tafamidis has demonstrated a sustained disease-modifying effect over 30 months, a period of time representing approximately 25% of the average TTR-FAP disease duration of 10 years.

Tafamidis has not specifically been evaluated in patients with renal impairment. Tafamidis is primarily metabolized by glucuronidation and excreted via the hepatobiliary pathway. The effects of creatinine clearance on tafamidis pharmacokinetics (PK) were evaluated in the population PK analysis in patients with creatinine clearance >30 mL/min. Pharmacokinetic estimates indicated no difference in steady-state clearance of tafamidis in patients with creatinine clearance <80 mL/min compared to those with creatinine clearance >80 mL/min. Therefore, dosage adjustment in patients with mild to moderate renal impairment is not necessary. No data are available in patients with severe renal impairment (≤30 mL/min).

Pharmacokinetic data indicated decreased systemic exposure (approximately 40%) and increased total clearance (0.52 L/h vs. 0.31L/h) of tafamidis in patients with moderate hepatic impairment (Child-Pugh Score of 7-9 inclusive) compared to healthy subjects. As patients with moderate hepatic impairment have lower TTR levels than healthy subjects, dosage adjustment is not necessary as the stoichiometry of tafamidis with its target protein TTR would be sufficient for stabilization of the TTR tetramer in these patients. The exposure in patients with severe hepatic impairment is unknown.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigators Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

- To obtain additional, long-term, open-label safety and efficacy data for tafamidis (Fx-1006A) in subjects with TTR-FAP.

- To continue to provide the investigational product tafamidis (Fx-1006A) to subjects with TTR-FAP who have completed Protocol Fx-006 or Protocol Fx1A-201.

2.2. Endpoints

The efficacy endpoints for this study are:

- The Neuropathy Impairment Score (NIS);

- The Total Quality of Life (TQOL) score as measured using the Norfolk Quality of Life for diabetic neuropathy (QOL-DN) questionnaire;

- The Karnofsky Performance Scale Index;

- Assessment of subject ambulation.

The safety endpoints for this study are:

- The incidence of treatment-emergent adverse events (TEAEs), physical examinations, clinical laboratory testing, use of concomitant medications, ECGs and vital signs

3. STUDY DESIGN

This is a Phase 3, open-label study designed to obtain additional long-term safety and efficacy data for once-daily tafamidis (20 mg soft gel capsule). In addition, this study will continue to provide subjects with tafamidis who have completed either Protocol Fx-006 (a 1-year, open-label extension study to Protocol Fx-005 which is a randomized, double-blind, placebo-controlled, 18-month study to evaluate the safety and efficacy of tafamidis) or Protocol Fx1A-201 (a Phase 2, open-label study to evaluate TTR stabilization,

safety and tolerability of tafamidis) for up to 10 years or until subject has access to tafamidis for TTR-FAP via prescription. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. Such subjects will be considered study completers. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor (see Section 6.3). CCI [redacted]

3.1. Rationale for Study Design and Control Group

This is an open-label study designed to obtain additional safety and efficacy data and to continue to provide tafamidis to subjects who have not had a liver or heart transplant and who have completed either Protocol Fx-006 or Protocol Fx1A-201. A control group is not applicable to this open-label study design.

3.2. Study Duration and Dates

The study will continue for up to 10 years or until subject has access to tafamidis for TTR-FAP via prescription. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor (see Section 6.3).

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

- Subject has successfully completed either Protocol Fx-006 or Fx-1A-201.

- If female, subject is post-menopausal, surgically sterilized, or willing to use an acceptable method of birth control (ie, hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide) throughout the study and for 3 months from the end of the study. (A condom alone is not considered an acceptable method of birth control.)

- Male or female subjects with TTR-FAP who have not undergone liver or heart transplantation at time of enrollment and who have successfully completed Protocol Fx-006 or Protocol Fx1A-201.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subject has not successfully completed either Protocol Fx-006 or Fx1A-201.

2. Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 3 to 4 times/month. The following NSAIDs are allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.

3. If female, subject is pregnant or breast feeding.

4. Clinically significant medical condition that, in the opinion of the investigator, would place the subject at an increased risk to participate in the study.

5. An ALT and AST value >3X ULN that in the medical judgment of the investigator is due to reduced liver function or active liver disease.

6. The subject has received a liver or heart transplant at time of enrollment.

7. Sexually active males with partners of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for at least 3 months after last dose of investigational product

4.3. Life Style Guidelines

4.3.1. Contraception

Females must be postmenopausal, surgically sterilized or willing to use two acceptable methods of birth control. All female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use two effective method of contraception consistently and correctly for the duration of the active treatment period and for 3 months after the last dose of investigational product. The investigator, in consultation with the subject, will select the most appropriate method of

contraception for the individual subject (ie,: hormonal contraception, intra-uterine device, diaphragm with spermicide, condom with spermicide; a condom alone is not considered an acceptable method of birth control). The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

All sexually active male subjects with partners of childbearing potential must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 3 months after the last dose of investigational product. The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This is an open-label, single-treatment study. All enrolled subjects will be assigned to receive a single oral daily dose of 20 mg Tafamidis.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Tafamidis meglumine (tafamidis), d-glucitol, 1-deoxy-1-(methylamino)-, 2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylate (1:1), is the salt form of 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid, or tafamidis (Fx-1006), the free acid. The only active ingredient in tafamidis meglumine is tafamidis.

The tafamidis meglumine drug product will be supplied by the Sponsor as opaque 12 oblong soft gelatin capsules filled with a suspension containing 20 mg of tafamidis meglumine.

Investigational product will be supplied in 10-count child resistant blisterpacks. Investigational product labels will contain the appropriate country-specific information in accordance with relevant regulatory requirements.

5.2.2. Preparation and Dispensing

Investigational product will be dispensed to subjects according to the following schedule:

- On Day 0 (Baseline), an initial 3-month supply of investigational product will be dispensed to subjects at the clinical unit. Subjects will take their first dose of investigational product at home beginning on Day 1 (ie, first dose).

- At 3-month intervals between clinic visits, 3-month supplies of investigational product will be mailed from the clinical site directly to subjects at home.

- Every 6 months, subjects will return to the clinical unit and will be instructed to bring all investigational product and packaging with them to determine investigational product compliance and accountability. At these clinic visits, 3-month supplies of investigational product will be dispensed directly to subjects for self-administration at home.

5.2.3. Administration

All enrolled subjects will self-administer a once-daily oral dose of 20 mg tafamidis at home as instructed by the clinical staff. All investigational product is to be taken by mouth, with water. Subjects will be instructed to take investigational product at the same time each day throughout the treatment period.

Medication errors may result, in this study, from the administration or consumption of the drug by the subject at the wrong time, or at the wrong dose strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRFs and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the product.

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to ADVERSE EVENT REPORTING section for further details).

5.2.4. Compliance

All investigational product will be self-administered by subjects at home. Subjects should be instructed to bring all investigational product and packaging to each follow-up visit to the clinical unit every six months. Compliance to investigational product will be determined through capsule counting procedures at subject visits to clinic. Compliance will be monitored and recorded in each subject's case report form (CRF). Additionally, investigational product accountability audits will be performed by the study monitor during routine monitoring visits.

5.3. Drug Storage and Drug Accountability

All investigational product (tafamidis) should be stored at controlled room temperature 15-25°C (59-77°F). Investigational product should be stored in its original package and should be protected from light.

Storage conditions stated in the SRSD (Investigator Brochure (IB),) may be superseded by the label storage.

Temperature of storage conditions should be monitored using validated devices that record maximum and minimum temperatures, are regularly calibrated, and data are regularly recorded. Should the product experience temperature excursion, relative to label instruction, during storage, then the impact to product quality and use should be addressed with relavant subject matter experts and documented accordingly.

Occasional short-term excursions from the intended storage conditions may occur. If the duration is short and the deviation in temperature is small, an investigation into the quality of the product is generally not required.

Subjects should be reminded of the storage conditions when drug is dispensed.

5.4. Concomitant Medication(s)

5.4.1. Allowed Medications

On Day 0, in conjunction with the review of their medical history, all subjects will be asked what medications they are taking. Thereafter, subjects will be asked what medications they have been taking at 3-month intervals (ie, during clinic visits every 6 months and via telephone contact at 3-month intervals between clinic visits). All concomitant medications will be recorded on the CRF.

5.4.2. Medication Restrictions

The following medications and substances are prohibited during the study, as specified below:

- Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 3-4 times/month. The following NSAIDs are allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.

Of note, in the presence of tafamidis, the plasma protein binding of prednisone was decreased by approximately 10%. As prednisone is rapidly metabolized to the active metabolite, prednisolone, the clinical relevance of these findings are unknown.

6. STUDY PROCEDURES

Every effort should be made to ensure that scheduled visits are made and protocol required tests and procedures are completed as described. From time to time there may be circumstances, outside of the control of the investigator, which may not make a clinic visit possible. In these cases, and with prior discussion and approval from the sponsor, alternative options may be considered. Approved alternative study visit options will not be considered protocol deviations.

Study procedures are outlined in the Schedule of Activities.

6.1. Screening/Baseline Assessment

The end of study physical examination (including weight) and vital sign assessments from Protocols Fx-006 and Fx1A-201 will serve as Day 0 (Baseline) for Protocol Fx1A-303/B3461023 if these examinations were performed within 30 days of Day 0. If more than 30 days has passed between the final study visit of Protocols Fx-006 or Fx1A-201 and Day 0 (Baseline) for Protocol Fx1A-303/B3461023, all Day 0 study procedures will be performed (ie, no data from the final study visits from the previous studies will be utilized). For subjects who successfully completed Protocol Fx1A-201, the NIS, Norfolk QOL-DN, and Karnofsky scores from the end of study visit of Protocol Fx1A-201 will serve as Day 0 (Baseline) assessments for Protocol Fx1A-303/B3461023 if these procedures were performed within 30 days of Day 0. For subjects who successfully completed Protocol Fx-006, the Norfolk QOL-DN from the end of study visit from Protocol Fx-006 will serve as Day 0 (Baseline) if it was performed within 30 days of Day 0. In addition, the cranial nerve and upper limb components of the NIS will be performed on Day 0 and combined with the NIS-LL data from the end of study visit from Protocol Fx-006 and the Karnofsky Performance Scale Index will be assessed on Day 0 of Protocol Fx1A-303/B3461023.

Subjects will be required to sign an informed consent form before beginning participation in Protocol Fx1A-303/B3461023. The following procedures will be performed on Day 0:

- All inclusion and exclusion criteria will be reviewed to ensure eligibility for participation in this study;
- Demographics (date of birth, age, gender, and race) for all subjects will be collected;
- A complete medical history will be obtained;
- Urine test for pregnancy (women of child bearing potential only);
- Complete physical exam including weight and vital signs (if not conducted within 30 days of Day 0);
- NIS;

- For subjects who completed Fx1A-201, only if not performed within 30 days of Day 0;

- For subjects who completed Fx-006, the cranial nerve and upper limb components will be performed on Day 0 and combined with the NIS-LL from end of study visit from Fx-006, if performed within 30 days of Day 0. Otherwise all three components of NIS will be performed on Day 0.

- Norfolk QOL-DN, only if not performed within 30 days of Day 0.

- Karnofsky Performanceperformance Scale Index.

  - For subjects completing Fx1A-201, only if not performed within 30 days of Day 0.

- Adverse events;

- Concomitant medications;

- Dispense 3 month supply of investigational product with instructions that subject is to administer the first dose at home on the following day as instructed (Section 5.2.3).

6.2. Study Period

6.2.1. Months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, 105, 111, 117

Subjects will be contacted by telephone, contact is to be made ± 1 week of scheduled time:

- Assessment of ambulatory status (mPND);

- Ask subjects non-leading questions such as “How do you feel?” and document adverse events;

- Record concomitant medications;

- Ask about possibility of pregnancy;

- Mail 3 month supplies of investigational product following telephone contact;

- These telephone visits can be conducted in person at the clinic at the discretion of the sites.

6.2.2. Months 6, 18, 30, 42, 54, 66, 78, 90, 102, 114

Subjects will return to the clinic for the following assessments. Visits are to occur ± 2 weeks of the scheduled time:

- Collect blood/urine samples for laboratory assessments (section 7.3);
- Urine pregnancy test (for women of childbearing potential);
- Assessment of ambulatory status (mPND);
- Ask subjects non-leading questions such as "How do you feel?" and record adverse events;
- Record concomitant medications;
- Determine drug compliance and accountability;
- Dispense 3 month supply of investigational product.

6.2.3. Months 12, 24, 36, 48, 60, 72, 84, 96, 108

Subjects will return to the clinic for the following assessments. Visits are to occur ± 2 weeks of the scheduled time:

- Perform abbreviated physical exam and measure vital signs;
- Collect blood/urine samples for laboratory assessments (section 7.3);
- ECG;
- Urine pregnancy test (for women of childbearing potential);
- Assessment of ambulatory status (mPND);
- Perform NIS;
- Administer Norfolk QOL-DN;
- Determine Karnofsky Performance Scale Index;
- Ask subjects non-leading questions such as "How do you feel?" and record adverse events;
- Record concomitant medications;
- Determine drug compliance and accountability;

- Dispense 3 month supply of investigational product.

6.2.4. End of Study Visit

The end of study visit will occur upon subject withdrawal from the study or upon subject completion, which will be up to 10 years or until subject has access to tafamidis for TTR-FAP via prescription. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor (see Section 6.3), subject withdrawal (for any reason), or program discontinuation by the Sponsor. The following activities will be completed:

- Complete physical examination, weight and vital signs, including assessment of the following body systems: general appearance, head and neck, eyes, ears, nose, throat, respiratory, genitourinary, endocrine, cardiovascular, abdomen, skin, musculoskeletalmuscoluskelatal, neurological, immunologic/allergies, hematologic/lymphatic;
- ECG;
- Urine pregnancy test (for women of childbearing potential) and determination of pregnancy;
- Assessment of ambulatory status (mPND);
- Perform NIS;
- Administer Norfolk QOL-DN;
- Determine Karnofsky Performance Scale Index;
- Ask subjects non-leading questions such as “How do you feel?” and record adverse events;
- Electrocardiogram (unless performed within 6 months prior);
- Collect blood/urine samples for laboratory assessments (Section 7.3);
- Record concomitant medications;
- Determine drug compliance and accountability.

In the event a subject is unable to return to the study site for the end of study visit, telephone contact with the subject approximately 30 days after the last dose of medication to assess adverse events and concomitant medications and treatments is expected. If laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at an institution local to the subject is acceptable.

The outcome of adverse events with a date of onset during the study period should be reevaluated, and any new adverse events should be recorded. All serious adverse events, and those non-serious adverse events assessed by the investigator as possibly related to study drug should continue to be followed even after subject withdrawal from study. These adverse events should be followed until they resolve or until the investigator assesses them to be "chronic" or "stable". Additional information on ADVERSE EVENT REPORTING can be found in Section 8.

6.3. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. In addition, the Sponsor may choose to discontinue this study, at which time all subjects will be withdrawn.

A subject may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent;
- Adverse event;
- Protocol noncompliance;
- Subject lost to follow-up;
- Subject death.

Subjects who are prematurely withdrawn from the study will not be replaced. Subjects who discontinue from the study at any time following enrollment will have a final end of study visit performed, including all safety and efficacy assessments, at the time of discontinuation.

Subjects undergoing liver and or heart transplantation while participating in this study will no longer receive investigational product. However, subjects who do undergo a liver transplant will not be withdrawn from this study and will be asked to return to the clinical unit post-transplantation on an annual basis for NIS, Norfolk QOL-DN, and Karnofsky Performance Scale Index evaluations, safety assessments, and to assess subject ambulation. Further relevant information for the Investigator to consider for any subject undergoing liver transplantation is provided in Appendix 4.

Upon regulatory approval of tafamidis for the treatment of TTR-FAP in their respective country, and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor. Subjects will have all end of study procedures completed prior to study withdrawal. These subjects are considered completers.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy Assessments

The NIS, Norfolk QOL-DN, and Karnofsky Performance Scale Index evaluations will be performed on an annual basis when subjects return to the clinical unit for study visits (ie, every other 6-month visit).

For subjects who successfully completed Protocol Fx1A-201, the NIS, Norfolk QOL-DN, and Karnofsky scores from the end of study visit of Protocol Fx1A-201 will serve as Day 0 (Baseline) assessments for Protocol Fx1A-303/B3461023 if these procedures were performed within 30 days of Day 0. For subjects who successfully completed Protocol Fx-006, the Norfolk QOL-DN from the end of study visit from Protocol Fx-006 will serve as Day 0 (Baseline) if it was performed within 30 days of Day 0. In addition, the cranial nerve and upper limb components of the NIS will be performed on Day 0 and combined with the NIS-LL data from the end of study visit from Protocol Fx-006 and the Karnofsky Performance Scale Index will be assessed on Day 0 of Protocol Fx1A-303/B3461023.

Refer to Appendix 1, Appendix 2, and Appendix 3, respectively, for the NIS, Norfolk QOL-PN, and Karnofsky Performance Scale Index efficacy evaluation forms.

The ambulatory status for each subject will be determined by the Investigator at each 6-month visit to the clinic as well as during telephone follow-up at 3-month intervals between clinic visits. The following scale, the modified polyneuropathy disability (mPND) score, will be used by clinical site staff to evaluate subject ambulation:

Score	Definition
0	Normal
I	Sensory disturbances in feet but able to walk without difficulty
II	Some difficulties walking but can walk without aid
IIIa	Able to walk with 1 cane or crutch
IIIb	Able to walk with 2 canes or crutches
IV	Not ambulatory; confined to wheelchair or bedridden

Source: (Suhr, 1995; Sharma, 2003) [9, 10]

7.2. Pregnancy

The end of study visit urine pregnancy test from Protocols Fx-006 and Fx1A-201 will be used as Day 0 (Baseline) for Protocol Fx1A-303/B3461023. If the pregnancy test is positive, the subject will be disallowed. Female subjects of child-bearing potential will be re-tested for pregnancy at every 6-month visit to the clinical unit and will be asked via telephone contact of possible pregnancy at 3-month intervals between clinic visits. A positive pregnancy test will lead to immediate discontinuation of investigational product and from the study. Subjects will also be instructed to notify the site should they become pregnant. In the event of a pregnancy, all investigational product must be discontinued immediately.

7.3. Clinical Laboratory Tests

The following laboratory parameters will be assessed upon the subjects return to the clinical unit every 6 months:

Serum chemistry	
Sodium	Globulin
Potassium	Alkaline phosphatase
Chloride	AST
Bicarbonate	ALT
Blood urea nitrogen	Gamma glutamyl transferase
Creatinine	Cholesterol
Calcium	Uric acid
Inorganic Phosphorous	Thyroid-stimulating hormone
Glucose	Total thyroxine (T4)
Total bilirubin	Free T4
Total proteins	Prealbumin (transthyretin)
Albumin	Retinol-binding protein
NT-pro-BNP	Troponin I

Coagulation	
Prothrombin time	INR

Hematology	
Hemoglobin	Platelets
Hematocrit	White blood cell count
Red blood cell count	Neutrophils
Packed cell volume	Lymphocytes
Mean corpuscular volume	Monocytes
Mean corpuscular hemoglobin	Eosinophils
Mean corpuscular hemoglobin concentration	Basophils

Urinalysis	
pH	Blood (free Hb)
Protein	Nitrite
Glucose	Urobilinogen
Ketones	Specific gravity
Bilirubin	

A central laboratory will be used to assess the parameters above. A manual will be provided to the sites describing the sample collection, storage, and shipping process. Approximately 8 mLs of blood will be collected at every visit when the laboratory parameters listed above are assessed.

The staff at the clinical unit will be instructed to review the source documentation (ie, central laboratory reports). For any abnormal laboratory result, the Investigator will be instructed to determine whether the result is “clinically significant” or “not clinically significant” by entering “CS” or “NCS”, respectively, directly on to source documentation. If an abnormal laboratory result is assessed as CS, then a corresponding AE should be recorded in the CRF.

7.4. Electrocardiograms

During the trial, a 12-lead ECGs will be performed every 12 months. The following ECG parameters will be assessed: PR, RR, PRS, QT, QTc interval, heart rate and overall interpretation. Each ECG will be recorded and reviewed locally by the Investigator.

7.5. Physical Examinations and Vital Signs

The end of study physical examination (including weight) and vital sign assessments from Protocols Fx-006 and Fx1A-201 will serve as Day 0 (Baseline) for Protocol Fx1A-303/B3461023 if these examinations were performed within 30 days of Day 0. An abbreviated physical examination (including weight and vital signs) will be conducted at every other 6-month visit to the clinical unit.

For blood pressure and pulse, measurements will be taken lying and standing.

7.6. Adverse Events

Starting from the date the informed consent form is signed, adverse events (AEs) will be recorded in the CRF and monitored throughout the study. All adverse events should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). All AEs will be recorded on the CRF. Definitions, documentation, and reporting of AEs are described in Section 8.

7.7. Concomitant Medications

On Day 0, in conjunction with the review of their medical history, all subjects will be asked about the medications they are taking. Thereafter, subjects will be asked about the medications they have been taking at 3-month intervals (ie, during clinic visits every six months and via telephone contact at 3-month intervals between clinic visits). All concomitant medications will be recorded on the CRF.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Should an investigator be made aware of any SAE occurring any time after the active reporting period, it must be promptly reported.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;

- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breast feeding;
- Medication error.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥ 3X the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2X ULN or not available. For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3X ULN, or ≥8X ULN (whichever is smaller).
- **Concurrent with**
    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥3X ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/(INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of

ethanol, acetominophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);

- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to

investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero [EIU] occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EIU Form.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as serious adverse events follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg,. follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.

8.10. Withdrawal Due to Adverse Events (See Also Section 6.3)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.12.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

There is no formal sample size calculation for this protocol. Subjects who completed Protocols Fx-006 and Fx1A-201 are eligible for this study; up to 110 subjects are expected to enroll in Protocol Fx1A-303/B3461023.

9.2. Efficacy Analysis

Both safety and efficacy data will be summarized using descriptive statistics. For continuous variables, mean, standard deviation, median, and ranges will be presented; for categorical variables, counts, and percentages will be presented. Safety and efficacy data collected will also be presented in data listings.

Subjects who enroll into the study and receive any amount of investigational product will be included in the safety population. Subjects who receive any amount of investigational product and have at least one post-baseline efficacy assessment will be included in the efficacy population.

9.2.1. Analysis of Primary Endpoint

9.2.2. NIS-LL

NIS-LL data will be calculated using the NIS scoring manual (Appendix 1). Change from Baseline for NIS-LL data (including data from this protocol and parent Protocols Fx-005, Fx-006, and Fx1A-201) will be analyzed using a mixed model analysis with baseline value as covariate, subjects as random effect, and time as fixed effect. NIS-LL data will be summarized by each scheduled assessment and a graphical presentation of these data will be presented.

9.2.3. NIS

NIS data will be calculated using the NIS scoring manual (Appendix 1). Change from Baseline for NIS data (including data from this protocol and Protocol Fx1A-201) will be analyzed using a mixed model analysis with baseline value as covariate, subjects as random effect, and time as fixed effect. NIS data will be summarized by each scheduled assessment and a graphical presentation of these data will be presented.

9.2.4. Norfolk QOL-DN

Quality of life (QOL) data will be calculated using the Norfolk QOL-DN scoring manual (Appendix 2). Change from Baseline for Norfolk QOL-DN data (including data from this protocol and parent Protocols Fx-005, Fx-006, and Fx1A-201) will be analyzed a using mixed model analysis (with baseline value as covariate, subjects as random effect, and time as fixed effect) to demonstrate the long term effects of tafamidis on QOL. Also, QOL data will be summarized by each schedule assessment and a graphical presentation of these data will be presented.

9.2.5. Karnofsky Performance Scale Index

The Karnofsky Performance Scale Index will be assessed for each subject at every other 6-month visit to the clinical unit. The Karnofsky Performance Scale Index allows subjects to be classified as to their functional impairment. This tool can be used to compare effectiveness of different therapies and to assess the prognosis in individual subjects; the lower the Karnofsky score, the worse the survival for most serious illnesses. The Karnofsky Performance Scale Index is provided in Appendix 3.

9.2.6. Ambulatory Status

Ambulatory status for each subject will be determined by the Investigator using the mPND score (Section 7.1). The determination of ambulatory status will occur at each 6-month visit to the clinic as well as during telephone follow-up at 3-month intervals between clinic visits. Results for subject ambulation will be summarized by visit and will be provided in data listings. Refer to the statistical analysis plan for further details.

CCI [redacted]

9.4. Demographics and Baseline Characteristics

Demographics and Baseline data (medical history, age, gender, race, weight, and height) will be summarized using descriptive statistics or frequency distributions, as appropriate.

9.5. Physical Examination and Vital Signs

Physical examinations and vital signs (lying and standing blood pressure and pulse; and respiratory rate and temperature) will be summarized using descriptive statistics or frequency distributions, as appropriate.

9.6. Clinical Laboratory Testing

See Section 7.3 for laboratory parameters for this study. All laboratory data will be presented in by-subject data listings. Abnormal laboratory values meeting potentially clinically significant (PCS) criteria will be analyzed. Laboratory PCS results and values outside the normal range will be flagged in the listings. Refer to the statistical analysis plan for further analysis details.

9.7. Adverse Events

All AE data collected on the CRF will be presented in summary tables and data listings.

9.8. Concomitant Medication

All data on concomitant medication usage collected on the CRF will be presented in summary tables and in data listings.

9.9. Pregnancy

Results from pregnancy testing will be presented in data listings.

9.10. ECGs

ECGs will be reviewed and summarized. ECG data will be presented in data listings.

9.11. Interim Analysis

Given the lack of long-term data in TTR-FAP, interim analyses will be performed during the course of the study to allow for the reporting of safety and efficacy data to the scientific community through presentation at scientific and professional meetings.

9.12. Data Monitoring Committee

This study will not use a Data Monitoring Committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of Tafamidis at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 28 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the CSA.

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Blake CC, Geisow MJ, Oatley SJ, Rerat B, C. Rerat. Structure of Prealbumin: Secondary, Tertiary, and Quaternary Interactions Determined by Fourier Refinement at 1.8 A. J Mol Biol. 1978; 121: 339-356.

2. Monaco HL, Rizzi M, Coda A. Structure of a Complex of Two Plasma Proteins: Transthyretin and Retinol-Binding Protein. Sci. 1995; 268: 1039-1041.

3. Nilsson SF, Rask L, Peterson PA. Studies on Thyroid Hormone-Binding Proteins. II. Binding of Thyroid Hormones, Retinol-Binding Protein, and Fluorescent Probes to Prealbumin and Effects of Thyroxine on Prealbumin Subunit Self Association. J Biol Chem. 1975; 250: 8554-8563.

4. Hammarstrom P, Jiang X, Hurshman AR, Powers ET, Kelly JW. Sequence-Dependent Denaturation Energetics: A Major Determinant in Amyloid Disease Diversity. Proc Natl Acad Sci USA. 2002; 99 Suppl 4: 16427-16432.

5. Quintas A, Vaz DC, Cardoso I, Saraiva MJ, Brito RM. Tetramer Dissociation and Monomer Partial Unfolding Precedes Protofibril Formation in Amyloidogenic Transthyretin Variants. J Biol Chem. 2001; 276: 27207-27213.

6. Colon W, Kelly JW. Partial Denaturation of Transthyretin is Sufficient for Amyloid Fibril Formation In Vitro. Biochemistry. 1992; 31: 8654-8660.

7. Adams D, Samuel D, Goulon-Goeau C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. Brain. 2000;123(7):1495-1504.

8. Sousa A, Coelho T, Barros J, et al. Genetic epidemiology of familial amyloidotic polyneuropathy (FAP)-type I in Póvoa do Varzim and Vila do Conde (North of Portugal). Am J Med Genet. 1995;60:512-521.

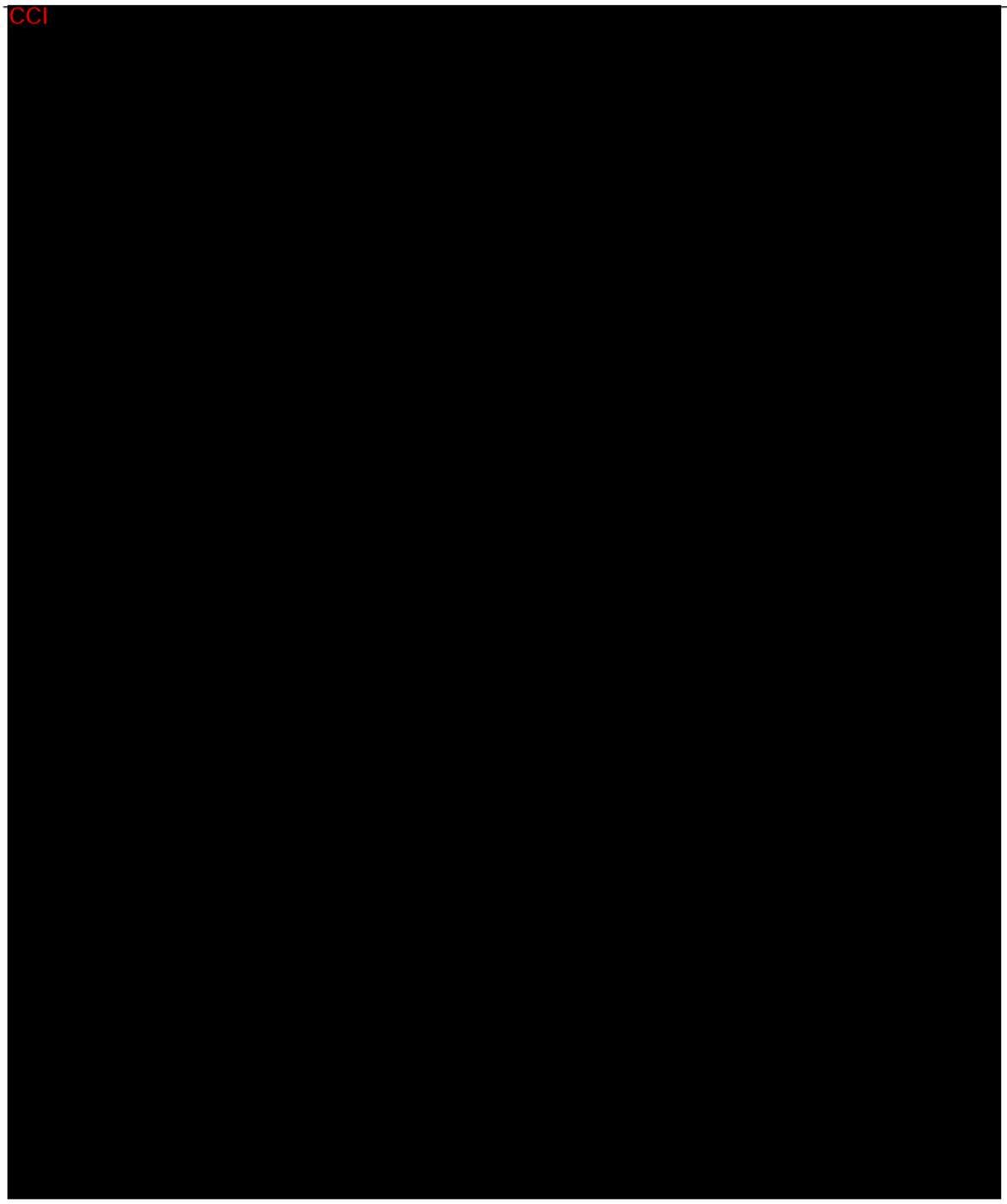
9. Suhr O, Holmgren G, Steen L, Wikstrom L, Norden G, Friman S, et al. Liver Transplantation in Familial Amyloidotic Polyneuropathy. Transplantation. 1995;60(9):933-8.

10. Sharma P, Perri R, Sirven J, Zeldenrust S, Brandhagen D, Rosen C, et al. Outcome of Liver Transplantation for Familial Amyloidotic Polyneuropathy. Liver Transplantation. 2003;9(12): 1273-80.

CCI [redacted]

CCI [redacted]

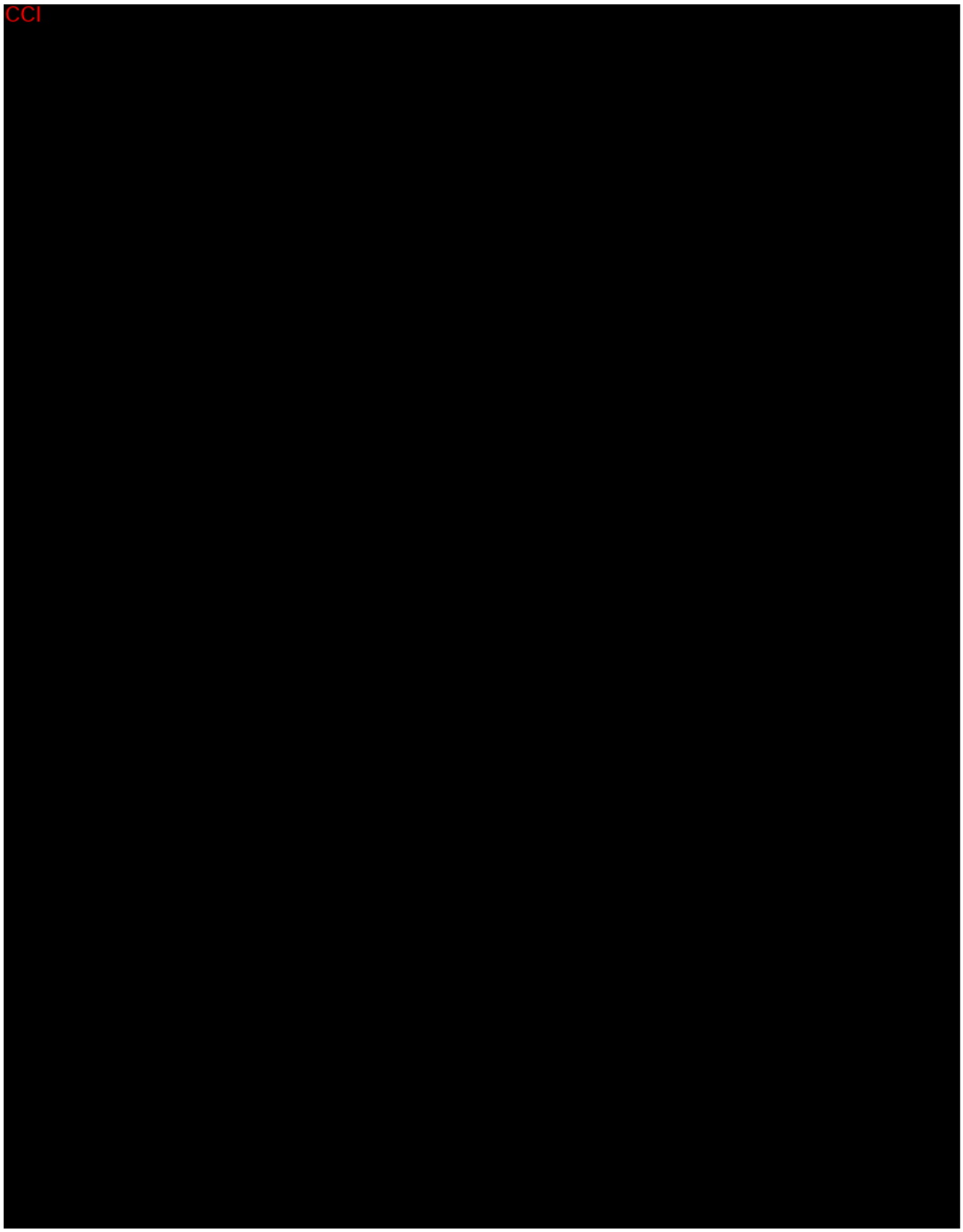
CCI



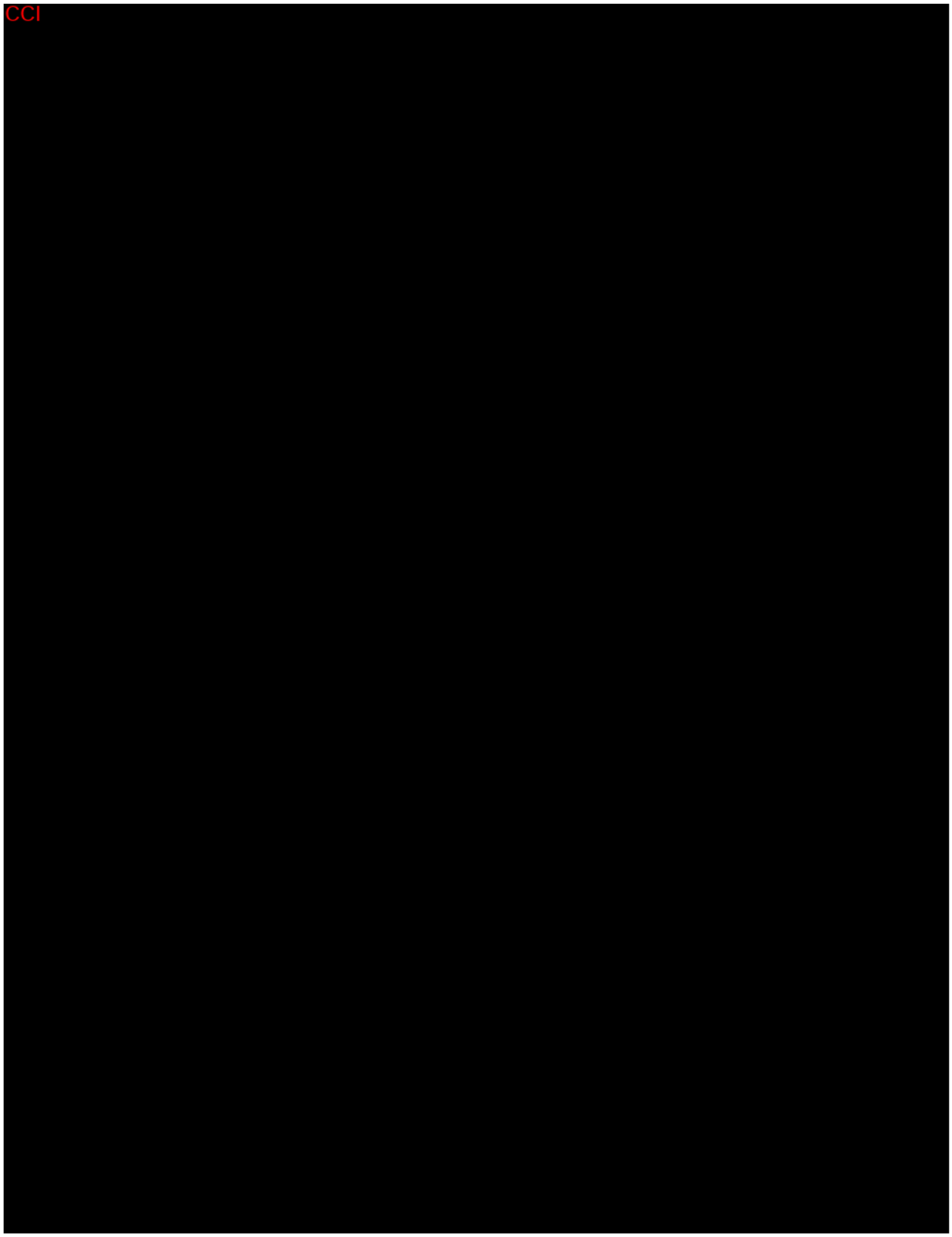
CCI [redacted]

CCI [redacted]

CCI



CCI



CCI [redacted]

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

CCI

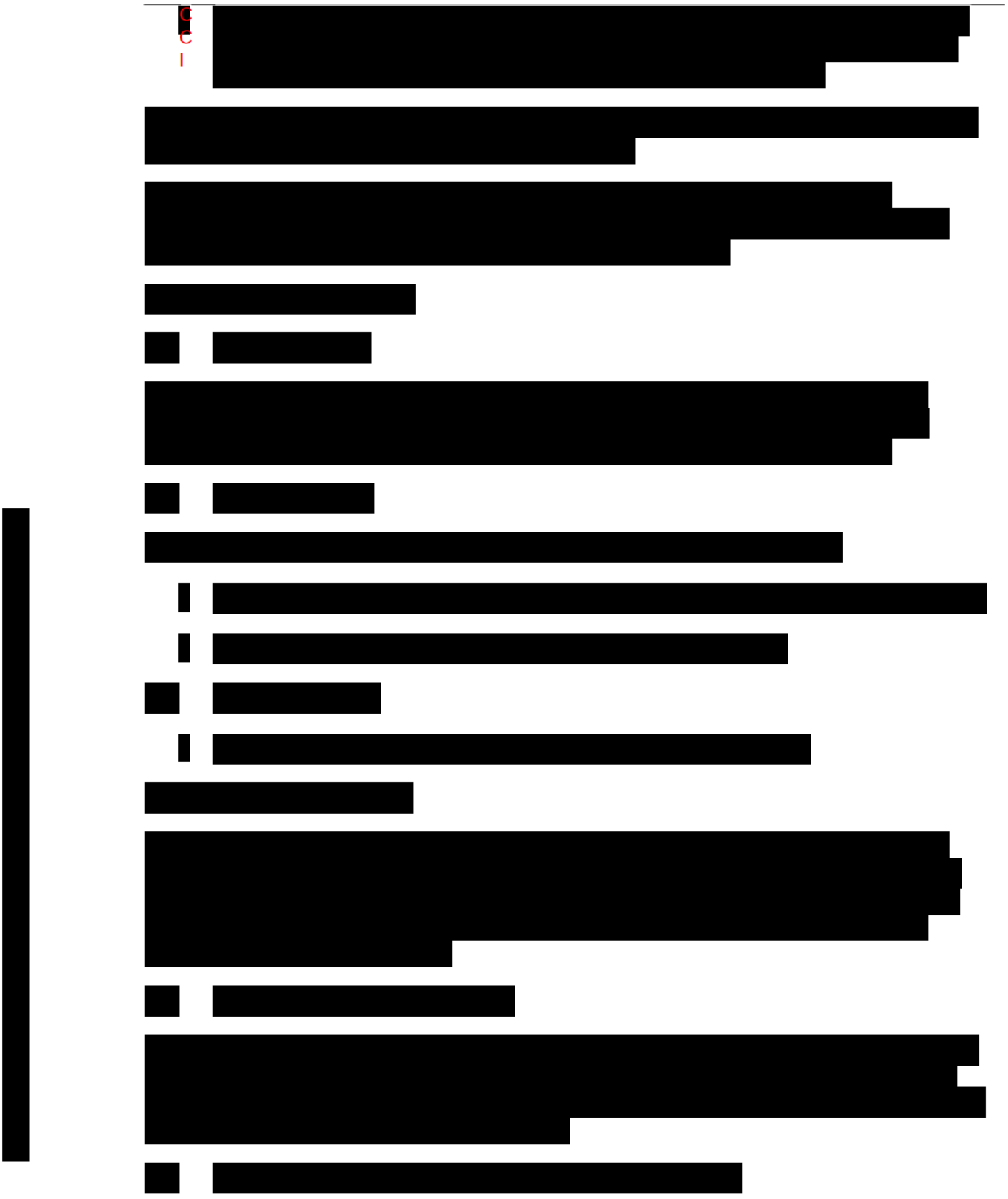
[redacted]

CCI

[redacted]

CCI

[redacted]



CCI

[redacted]

CC
I

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]